NON-TECHNICAL ABSTRACT

PHASE I/II STUDY OF ALLOGENEIC HUMAN GM-CSF GENE TRANSDUCED PROSTATE CANCER VACCINES IN PATIENTS WITH METASTATIC PROSTATE CARCINOMA

No systemic therapy is curative for metastatic prostate cancer (PCA). Prostate cancer is now the second most common cause of death from cancer in the US with an American dying on average every 15 minutes from metastatic disease. Interest in immunotherapy using gene therapy for PCA has been stimulated by the findings that cytokine transduced tumor vaccines can induce antitumor immune responses. We have conducted extensive laboratory studies using a strategy for inducing anti-tumor immune responses to non-immunogenic tumors including PCA. By inserting immunostimulatory genes into rodent tumor cells, and injecting them under the skin, systemic antitumor immune responses have been reproducibly induced, resulting in eradication of small amounts of implanted tumor at distant sites. The Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) gene in these model studies conferred the most potent antitumor effects so far compared to other cytokines tested. Efficient introduction of this gene in the model cancer vaccine cells was accomplished with the retroviral vector MFG-S. MFG-GM-CSF gene modified prostate cancer vaccines can cure animals with chemotherapy and hormone therapy resistant prostate cancer without apparent toxicity. Using the MFG-S vector, we are able to prepare allogeneic prostate cancer cell vaccines for patients who recur with advanced PCA after surgery, and do not have surgically resectable cancer for genetic modification as a vaccine. The genetically engineered prostate cancer vaccine cells then secrete GM-CSF in the range that confers antitumor efficacy. Lethal irradiation of the genetically engineered PCA cells does not diminish therapeutic effects of vaccine cells genetically engineered to secrete the GM-CSF gene in our published preclinical studies. Irradiation of tumor vaccines affords a measure of safety for human studies without compromising potential therapeutic efficacy.

The overall objective of the phase I portion of the study is to confirm the safety and tolerability of PCA allogeneic vaccine cell skin injections using a vaccine generated from two PCA cell lines genetically modified to highly express the GM-CSF gene. The vaccination cell dose has had minimal toxicities when irradiated tumor cells taken from patients have been used. These immortalized lines, LnCAP and PC-3, grow in tissue culture allow a virtually limitless supply of vaccine cells theoretically to over 40,000 US men diagnosed yearly who have metastatic prostate cancer, but do not have large enough tumors which can be resected safely. These two cell lines are also chosen as they posses the most molecular and antigenic similarities to metastatic prostate cancers. To help ensure safety, all tumor cell vaccines will be irradiated prior to injection. The rat prostate cancer genetically engineered tumor vaccines were effective at eliminating up to about 10,000 cancer cells at distant sites. The rodent tumors double every two days while human prostate cancers double every 80 to 100 days. In translation to clinical trial, patients with minimal metastatic tumor burdens will be treated to afford the highest likelihood of a remission. Patients will be vaccinated every week for eight weeks. The dose and schedule of vaccinations is in the range where MFG-GM-CSF gene modified renal cell carcinoma vaccines have shown preliminary evidence of efficacy without significant toxicity at Johns Hopkins. If safety is confirmed in the first 10,a phase II portion of the study will evaluate efficacy in up to 30 patients. The PCA specific blood test Prostate Specific Antigen can be used as a intermediate endpoint to test antitumor effects and duration of remissions in the phase II portion of the study.